Characteristics of Anterior Segment Dysgnesis in Pediatric and Strabismus Ophthalmology Unit at Cicendo Eye Hospital 2012-2014

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Abstract

Background: Developmental anomalies in congenital anomalies cause malformation, such as Anterior Segment Dysgenesis (ASD). Disorder in maturation of anterior segment of the eye occurs in ASD, associated with increased risk of glaucoma. This relation is not supported with enough data about characteristics pediatric patients with ASD in Indonesia. The aim of the study was to describe characteristics ASD in pediatric patient Cicendo Eye Hospital based on patients' identity, clinical profile and obstetrics profile.
Methods: This study used a descriptive method and conducted retrospectively. Data were collected from medical records of patient with ASD in Pediatric Ophthalmology and Strabismus Unit at Cicendo Eye Hospital, from January 2012 to December 2014. This study was conducted from July to November 2015. Total sampling based on inclusion criteria were used in this study. Statistic software was used to analyze data.
Results: This study used a descriptive method and conducted retrospectively. Data were collected from medical records of patient with ASD in Pediatric Ophthalmology and Strabismus Unit at Cicendo Eye Hospital, from January 2012 to December 2014. This study was conducted from July to November 2015. Total sampling based on inclusion criteria were used in this study. Statistic software was used to analyze data.
Conclusions: Characteristics pediatric patients with ASD at Cicendo Eye Hospital based on patients identity are mostly patients diagnosed in infant age group, from outside Bandung, and mostly boys. Based on clinical profile most diagnosis is congenital glaucoma, bilateral dominantly, and without complication. Based on obstetric profile most patients with ASD were born at term without difficulties. **[AMJ.2016;3(4):616–70]**

Keywords: Anterior segment dysgenesis, anterior segment of the eye, cicendo eye hospital, glaucoma congenitals

Introduction

Malformation occurs in congenital anomalies. It is the same with what occurs in Anterior Segment Dysgenesis (ASD). This malformation occurs during organogenesis, which is in the third up to eighth week of pregnancy.[1] Environmental and genetic factors affect malformation, which cause the incomplete development in structure, or loss of certain structures.[1,2]

The ASD involves the migration process and mesenchymal tissue differentiation, which makes anterior structure of the eye including iris, cornea, lens, and drainage structure. This anomaly affects the maturity of the functions for anterior segment of the eye. This condition enhances the risk of getting glaucoma, cataract, and the increased risk of corneal opacities.[3,4] The ASD has single type such as posterior embryotoxon, iris hypoplasia, corneal opacities, or the combination of the types which results in new diagnosis such as Axenfeld-Rieger Syndrome (ARA). This new diagnosis is the combination of iris hypoplasia, posterior embryotoxon, and/ or the adhesion of irido–cornea.[4]

The relation between ASD and other abnormalities is not supported by the presence of inadequate data about characteristics of ASD, especially in Indonesia. Therefore, the aim of study was to describe characteristics ASD based on patients' identity, clinical profile, and obstetric profile. Status national referral hospital of Cicendo Eye Hospital supports this

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study.[5]

Methods

This study used a descriptive method retrospectively. The samples of this study were taken from medical records secondary data of patients with ASD during the period of January 2012 to December 2014 in Pediatric Ophthalmology and Strabismus Unit at Cicendo Eye Hospital. This study was conducted from July to November 2015. This study was conducted after getting approval of collecting data from the President Director of the Cicendo Eye Hospital and the ethical approval from the Committee of Ethical Health Research of Faculty Medicine Universitas Padjajaran, No: 438/UN6.C1.3.2/KEPK/PN/2015.

This study used total sampling method. The inclusion criteria of this study were the medical record of pediatric patients with the range of age between 0–18 years old with diagnosis of ASD classifications, information about lateralization, visual acuity, complication, pregnancy history, age of pregnancy, delivery history, and the management. Exclusion criteria were damaged and/ incomplete data of the medical records.

Data collected then, were grouped into three characteristics. The first characteristic was based on the patients' identity such as age, gender, and address. The second characteristic was based on the clinical profile of the patient, which included the diagnosis, the type of diagnosis, lateralization, visual acuity, complication, and management. The third characteristic was based on the obstetric profile of the patient, which include pregnancy history, age of pregnancy, and delivery history. SPSS was used to analyzed data and presented in tables and charts.

Results

There were 99 data (n = 99 ASD patients) who met the inclusion criteria from the 125 medical records. There were 24 medical records, which were excluded due to the incomplete obstetric profile. First characteristics of ASD patients were characteristics based on patients' identities, included gender, age, address, and the diagnosis. Based on gender, the number of male patients was bigger than the female ones, which was 51.52% (n = 51 male patients) and 48.48% (n = 48 female patients) (Table 1).

Based on age group, ASD occurred more in patients who belong to infant group (28 days–12 months), (55.56% (n = 55 patients)). Based on their address, patients who came to Pediatric Ophthalmology and Strabismus

Table 1 Characteristics ASD Based on Patients' Identity

Patients' identity	Amount (n= 99)	Percentage (%)
Gender		
Boys	51	51.52
Girls	48	48.48
Age group		
Neonates (0–27 days)	9	9.09
Infant (28 days–12 months)	55	55.56
Toddler (13 months–3 years)	15	15.15
Early childhood (4–5 years)	11	11.11
Middle childhood (6-11 years)	8	8.08
Adolescent (12–18 years).[6]	1	1.01
Address		
Bandung City	21	21.21
Bandung District	6	6.06
Cimahi City	2	2.02
Outside Bandung	70	70.71

Table 2 Characteristics ASD Based on Clinical Profile

Type of diagnosis	Amount (n)	Percentage (%)
Single diagnosis	63	63.64
Multidiagnosis		
1 concomitant	22	22.22
2 concomitant	13	13.13
3 concomitant	1	1.01
Total	99	100

Unit at Cicendo Eye Hospital with ASD were mostly from out of Bandung, (70.71% (n = 70 patients)) (Table 1).

Second characteristics of ASD patient were characteristics based on clinical profiles included diagnosis, type of diagnosis, lateralization in eyes, systemic complication, examination of visual acuity, and the management. ASD abnormality was classified into 18 diagnoses, in the diagnosis profiles of the patients with ASD; they could have single diagnosis or multiple diagnoses.3,4The variation of diagnosis types results were 150 diagnoses from the total of 99 ASD patients in this study. Based on type diagnosis 63.64% (n = 63 patients) were diagnosed with single diagnosis, while 36.36% (n = 36 patients) were diagnosed with multiple diagnoses (Table 2).

Based on the medical records in Pediatric Ophthalmology and Strabismus Unit at Cicendo Eye Hospital, from 18 classifications of ASD diagnosis, there were 11 diagnoses which appeared in this study. They included ASD, iris hypoplasia, congenital glaucoma, ARA, limbal dermoid, congenital megalocorneal, microcornea, aniridia, Peter's anomaly, sclerocornea, and microphtalmos. Meanwhile, there were seven diagnoses which did not appear in this study which included posterior embryotoxon, congenital iris ectropion, congenital hereditary endothelial dystrophy, posterior polymorphous dystrophy, ICE Syndrome, cornea plana and autosomal dominant keratitis.

The distribution of 11 diagnoses presented in patients' characteristics based on their diagnosis profiles (Table 3). The most appearing diagnosis occurred in ASD patients in Pediatric Ophthalmology and Strabismus Unit at Cicendo Eye Hospital was congenital glaucoma, (30.67% (n= 46 diagnoses)). The distribution of other diagnoses presented (Table 3).

The distribution of diagnosis along with

Table 3 Characteristics ASD Based on Diagnosis Profile

Diagnosis profile	Number of Patients (n)	Percentage (%)
ASD*	14	9.33
Iris hypoplasia	2	1.33
Congenital glaucoma	46	30.67
ARA**	1	0.67
Limbal dermoid	2	1.33
CM***	3	2
Microcornea	19	12.67
Aniridia	3	2
Peter's anomaly	16	10.67
Sclerocornea	14	9.33
Microphthalmos	30	20
Total	150	100

Note: *Anterior Segment Dysgenesis (ASD); **Axenfeld Rieger Syndrome (ARA); ***Congenital Megalocornea (CM)

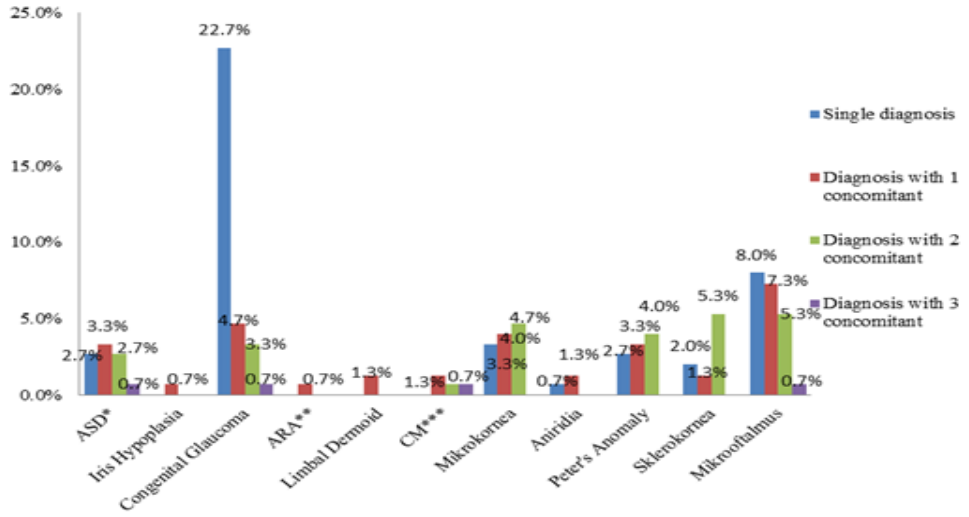

Figure 1 Distribution Diagnosis of ASD Along with Type of Diagnosis

Note: *Anterior Segment Dysgenesis (ASD); **Axenfeld Rieger Syndrome (ARA);***Congenital Megalocornea (CM).

the type of diagnosis described (Figure 1). Congenital glaucoma was mostly found single diagnosis, 22.7% out of the appearing total diagnoses. The diagnosis with one concomitant was microphtalmus, (7.3%). The diagnosis with two concomitant was microphtalmus and sclerocornea, (5.3%). Meanwhile, the diagnosis with three concomitant was the combination of each ASD diagnosis; congenital glaucoma, CM, and micropthalmos.

The lateralization in ASD patients' eyes were dominantly bilateral, (69.7% (n = 69 patients)) (Table 4). The examination of ASD patients' visual acuity mostly used single examination which was 68.7% (n = 68 patients), with the most type of examination was blink reflex (33.3% (n = 33 patients)) (Table 4).

In 99 ASD patients, there were 80.8% (n= 80 patients) who did not have systemic complication. Most patient with ASD were treated with single management 57.6% (n= 57 patients) (Table 4). The type of single management mostly done was conservative , which is 45% (n = 45 patients). Meanwhile, the combined management mostly used was surgical with medicamentosa which is 23% (n= 23 patients) (Table 4).

The third characteristics of ASD patients were characteristics based on obstetric profiles. The particular patients' obstetric profiles included pregnancy history, age of pregnancy, and delivery history (Table 5). Based on the pregnancy history, ASD patients dominantly had one obstacle during pregnancy, (80.8% (n= 80 patients)). There were 14.1% (n= 14 patients) who had two obstacles during pregnancy, and 5.1% (n= 5 patients) had three obstacles during pregnancy. The most appearing obstacle during ASD patients' pregnancy was the consumption of teratogenic medicines, (29.3% (n= 23 patients)) (Table 5).

Based on medical record, ASD patients were born mostly when the age of pregnancy was full term, (68.7% (n = 68 patients)). Based on the delivery history, ASD patients who obtained assistance from midwife were 67.7% (n = 67 patients). Based on the difficulty that the ASD patients faced during delivery, there were 83.8% (n = 83 patients) without any difficulty (Table 5).

Discussion

The ASD patient's characteristics based on their identities in Pediatric Ophthalmology and Strabismus Unit at Cicendo Eye Hospital revealed the number of male patients was higher than the female ones. Based on a study in Australia, the identification of PITX3 gene interpolation in ASD excludes the X-linked theory. However, the tendency of dominant gender which occurs in ASD needs further study because each region has its own variation.[9] Based on age category, ASD disease is diagnosed more in the age group of neonates (28 days–12 months), which is 55.56% (n= 55 patients). This is due to the

significant development from eyes occurs during 6 months of postnatal, including the visual behavior developing when babies are 6–8 weeks old. If the visual behavior of children has not appeared within the first three months, it indicates that consulting to

Table 4 Characteristics ASD Based on Clinical Profile

Clinical Profiles	Amount (n= patient)	Percentage (%)
Lateralization		30.3
Unilateral	30	69.7
Bilateral	69	100
Total	99	
Visual Acuity examination		
Single		33.3
Blink reflex	33	19.2
Fix and follow object/light	19	3
Decoration cake	3	3
Tumbling C/E	3	3
Wall chart	3	7.1
Others	7	
Combination		15.2
Blink Reflex& FF*	15	2
Blink Reflex & DC**	2	3
Blink Reflex &Others	3	6.1
FF*& Tumbling C/E	6	1
FF *& Wall chart	1	4
Wall chart & others	4	100
Total	99	
Systemic complication		19.2
Yes	19	80.8
No	80	100
Total	99	
Management		
Single		8.1
Medicamentosa	8	4
Surgical	4	45
Conservative	45	
Combination		23.2
Medicamentosa & Surgical	23	10.1
Medicamentosa & Conservative	10	2
Surgical & Conservative	2	7.1
Medicamentosa, Surgical and Conservative	7	
Total	99	100

Note: *Fix and Follow light/object (FF); **Decoration cake (DC)

eye specialist needs to be done immediately.[10] Based on the patients' addresses; they are dominantly from outside Bandung. This fact is supported by the status of the Cicendo Eye Hospital which becomes the national center of referral hospital.[5]

In pathophysiology of ASD, the mechanism of gene mutation can be dominantly autosomal, recessively autosomal, or both.[4] The gen that plays important role in pathophysiology of ASD can cause various manifestations. This particular manifestation in ASD can be in the form of visual disturbance or cosmetic disturbance with or without the visual disturbance itself. Meanwhile, the clinical profiles of ASD have the form of single anomaly and or associated by concomitant.[2,7,11] Type of diagnosis of ASD patients in Pediatric and Starbismus Unit of the Cicendo Eye Hospital is mostly the single diagnosis, which is 63.64% (n= 63 patients).

The characteristics of ASD patients based on their diagnosis profiles in This study found that there are 11 types of ASD classifications in 99 patients. The ASD is a combined diagnosis of which the clinical manifestation heterogeneous both in genotype and phenotype way. However, each of the type of classification of ASD has its own characteristic in relation with the origin of its embryology.[2,7] Classification of ASD appeared in 99 patients becomes a special variation in the sample taken from the Cicendo Eye Hospital.

There are 150 diagnoses in 99 patients ASD. The most appearing diagnosis in patients is congenital glaucoma, which is 30.67% (n= 45 diagnoses). This is because one of the genes playing role in pathophysiology of ASD lacks of CYPB1 gene. This very gene experiences mutation in congenital glaucoma. The existence of these genes' similarity stimulates congenital glaucoma appears frequently in ASD. One of the malformations caused by CYPB1 gene is trabecular dysgenesis. In the process, the flow of aqueous liquid is obstructed that resulting in increase of the IOP. Thus, the possibility of getting congenital glaucoma is increased up to 50%.[2,3,12]

The distribution of diagnosis types towards the appeared diagnoses in this study is presented, which shows in single diagnosis congenital glaucoma appeared dominantly in patients. Anterior Segment Dysgenesis is malformation which involves cornea, lens, and anterior space. In pathophysiology of congenital glaucoma, it occurs because of the increased intraocular pressure, which is caused by the imparity between the production of aqueous liquid by the ciliary body and the drainage to the anterior space. The high level of intraocular pressure also occur in microcornea anomaly, sclerocornea, Peter's anomaly, and ARA.[2,12] Meanwhile, microphtalmos diagnosis is the most diagnosis with 1–2 concomitant, followed by sclerocornea which is the most diagnosis with 2 concomitant. In micropthalmus pathophysiology, micropthalmus has gene with SOX2 dominant and PAX6, CHX10, OTX2 gene which play roles in micropthalmos formation in other anomalies such as sclerocornea, microcornea, iris hypoplasia, ARA, and Peter's anomaly. The same gene regulation can cause one patient likely develops micropthalmos and sclerocornea with same concomitant diagnosis.[7,12–14]

The lateralization characteristic in patients' eyes with ASD diagnosis is mostly bilateral, (69.7%). This is because there are three anomalies that mostly occurred in this study. Those are the dominantly bilateral anomalies; congenital glaucoma, micropthalmus, and microcornea.[3] In ASD anomalies appeared in this study, the existence of systemic complication is found. One of the forms of systemic concomitant condition is the slow development in children, abnormality in teeth (dental hypoplasia), and so forth. Based on medical record, there are 80.8% of ASD without systemic complications.

Based on medical record single most method used to examine visual acuity in ASD patient is blink reflex, (33.3%). This examination is mostly used due to the fact that patients with ASD diagnosis dominantly on age group of infant. The visual examination in this age group is still in the process of maturation; therefore, the most effective examination is by using the reflex towards light (blink reflex). In ASD management, the mostly with conservative method, that is up to 45%.

Congenital anomaly is caused by genetic material defect, teratogen reaction, or obstetric complication, which results in various clinical profiles.[5] Based on ASD patients' characteristics towards their obstetric profiles, it is found that there are 29.3% of patients consuming medicines during pregnancy, which is the most found obstetric factor. The type of medicines mostly consumed during pregnancy by the mother of ASD patients are antibiotics and herbal medicines. Based on previous study in Canada, there are correlation between consumption hydroxychloroquine, methotrexate, and 2-chloro-2'-deoxyadenosine into ASD formation.[15] Based on medical

records, infection (TORCH) and hypertension are two diseases mostly occur in patients' mother. In microphtalmos diagnosis, TORCH infection is a strong evidence of the interaction between external factors and micropthalmos occurrence.[6]

In ASD patients' obstetric profiles, the age of pregnancy mostly full term. The formation of anterior segment in embryology occurs in the twenty-second day of gestation until eighth month of gestation. However, the birth at normal term can still results in malformation if the genetic factor interacts with external factors.[2,4] The delivery history becomes one of the important things, knowing that troubles during maternity or lacking of hygiene can result in transmission of infection. Another possibility that can happen is lesion caused by the tools used by the paramedics when babies were difficult to deliver, for instance forceps lesion in cornea.[7] Based on the delivery history of ASD patients, those who were helped by midwife were 67.7% and 83.8% of ASD patients were born without facing any difficulties.

After conducting the study to determine characteristics of anterior segment dysgenesis in pediatric patients in the Cicendo Eye Hospital in the period of January 2012–December 2014, there are several conclusions. First, based on the patients' identity profiles, there are 99 samples obtained proportionally with the fact that male patients are more than female. Second, the diagnoses of ASD mostly occur in the age group of neonates. Third, diagnosed patients are dominantly from outside of Bandung.

Based on the clinical profiles, type of ASD diagnosis is mostly single diagnosis with the appeared ASD classification as much as 11 diagnoses. The most appeared diagnosis is congenital glaucoma, (30.67%).

In ASD patients' clinical profiles, the characteristic of ASD patients' eyes is dominantly bilateral and not accompanied by systemic complication. The dominance of ASD patients in this study is examined through their visual acuity by using blink reflex method. In this study, ASD patients are treated mostly by using conservative management.

Obstetric factors and gynecology are the factors which affect the congenital anomaly. Based on the pregnancy history of the ASD pediatric patients, this study found that consuming medicines or herbal medicines during pregnancy is mostly done by the patients' mothers. However, based on the age of pregnancy, the ASD pediatric patients were born full term, being helped by midwife, and faced no difficulties.

The ASD is a kind of disease which is related to the genetic material and external factors during pregnancy and maternity. Therefore, early precaution is needed, for instance by doing genetic counseling, screening, and routine antenatal examination that the risk of developing congenital disease can be minimized. Mothers need to increase their awareness towards their own health and the fetus' by paying attention to the nutrition, not consuming medicines or herbal medicines without consultation, and taking care of both their physical and psychological health optimally.

Referring to the picture of ASD in pediatric patients in the Cicendo Eye Hospital, the clinicians and paramedics need to be more knowledgeable in doing anamnesis, examining visual acuity and other supportive actions. This is needed due to the fact that the factors causing ASD can be detected earlier. The risk factors such as history of previous illnesses and obstetric history should be included in the inquiry list to the patients' parents or guardians.

It would be better to use standard abbreviations, which can be understood by both the clinicians and other paramedics for medical records. It is desirable that this study is published disseminated in order to improve the societies' knowledge and can be used to the further investigation. Analytical study can be done in further study, to see relation risk factor and pathophysiology of ASD.

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References

1. Sadler TW, editor. Langman's medical embryology. 12thed. Baltimore: Lippincot Williams & Wilkins; 2012. p. 329–38.
2. Idrees F, Vaideanu D, Fraser SG, Sowden JC, Khaw PT. A review of anterior segment dysgeneses. Surv Ophthalmol. 2006;51(3):213–31.
3. Sowden J. Moleculr and developmental mechanisms of anterior segment dygenesis. Eye. 2007;21(10):1310–18.
4. Reis LM, Semina EV. Genetics of anterior segment dysgenesis disorders. Curr Opin Opthalmol. 2011;22(5):314–336.
5. Pusat Komunikasi Publik, Sekertariat Jenderal Kementrian Kesehatan RI. Menkes resmikan RS Mata Cicendo sebagai pusat rujukan nasional. Depkes [Online Article] 2012 [cited 2012 May 12]. Available from:

http://www.depkes.go.id.
6. William K, Thomson D, Seto I, Contopoulos-Ioannidis DG, Ioannidis JP, Curtis S, et al. Standard 6: age groups for pediatric trials. Pediatrics. 2012;129(Suppl3):S153–60.
7. Guercio JR, Martyn LJ. Congenital malformation of the eye and orbit. Otolaryngol Clin North Am. 2007;40(1):113–40.
8. Hoyt CS, Taylor D, editors. Pediatric Ophtalmology and Strabismus. 3rded. London: Elsevier Health Sciences;2011. p. 244–63
9. Summer KM, Withers SJ, Gole GA, Piras S, Taylor PJ. Anterior segment mesenchymal dysgenesis in a large Australian family is associated with the recurrent 17bp duplication in PITX3. Mol Vis. 2008;14:2010–5.
10. Ramasubramanian A, Johnston S. Neonatal eye disorders requiring ophthalmology consultation. NeoReviews. 2011;12(4):e216–22.
11. Ito YA, Walter MA. Genomics and anterior segment dysgenesis: a review. Clin Exp Ophthal. 2014;42(1):13–24.
12. Wiggs JL. Genetic etiologies of glaucoma. Arch Ophthalmol. 2007;125(1);30–7.
13. Chassaing n, Causse A, Vigouroux A, Delahaye A, Alessandri JL, Boespflug-Tanguy O, et al. Molecular findings and clinical data in cohort of 150 patients with anopthalmia/micropthalmia. Clin Genet. 2014;86(4):326–34.
14. Verma AS, Fitzpatrick DR. Anopthalmia and micropthalmia. Orphanet J Rare Dis. 2007;2(2):47–52.
15. Mulholland CP, Pollock TJ. The Peters anomaly following antenatal exposure to methotrexate and hydroxychloroquine. Can J Ophthalmol. 2011;46(3):289–90.